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Blood Loss Kinetics During the First 12 Hours After On-Pump Cardiac Surgical Procedures

Marine Saour, MD, Norddine Zeroual, MD, Emmanuelle Aubry, MD, Cinderella Blin, MD, Philippe Gaudard, MD, PhD,* and Pascal H. Colson, MD*

Department of Anesthesiology and Critical Care Medicine, Arnaud de Villeneuve Hospital, Montpellier University Hospital Center, Montpellier, France; Department of Physiology and Experimental Medicine Heart Muscles, National Institute of Health and Medical Research (INSERM), National Center for Scientific Research (CNRS), Montpellier University, Montpellier, France; and Institute for Functional Genomics, National Institute of Health and Medical Research (INSERM), National Center for Scientific Research (CNRS), Montpellier University, Montpellier, France

Background. Anemia and coagulation management and a restrictive transfusion strategy are key points of blood management in patients undergoing cardiac surgical procedures. However, little consideration has been given to the kinetics of postoperative bleeding. This prospective observational study investigated bleeding kinetics from chest tubes to assess whether it was possible to predict, within the early postoperative hours, major bleeding at 12 postoperative hours.

Methods. Adult cardiac surgical patients who were admitted consecutively to the postoperative intensive care unit in a tertiary academic hospital from January to June 2016 were included. Blood volume was collected from the chest drains, and major bleeding was defined as bleeding exceeding the 90th percentile of the volume distribution at 12 postoperative hours. Receiver operating characteristics curve analysis was performed with hourly bleeding thresholds to determine the best predictor of major bleeding.

Results. In 292 patients, bleeding at 12 postoperative hours ranged from 60 to 2190 mL (median, 350 mL), and 30 patients had major bleeding, with a threshold of 675 mL. Bleeding volume declined logarithmically, 54% [IQR, 45% to 63%] within the first 4 hours. Patients with major bleeding had a higher bleeding volume every hour ($P < .004$). A good predictive value was observed within the first 2 hours (2.73 mL/kg; receiver operating characteristics area under the curve, 0.87 ± 0.04 [IQR, 0.79 to 0.94]; $P < .001$).

Conclusions. The hourly rate of chest tube blood loss seems to be relevant to predict, within the first postoperative hours after cardiac surgical procedures, major bleeding at 12 postoperative hours. Early detection of blood loss may help to improve a patient's blood conservation strategy because it may prompt preemptive treatments.

Postoperative bleeding in cardiac surgical procedures may increase morbidity and mortality, not only because of the vital risk in case of massive bleeding with hemorrhagic shock or cardiac shock with tamponade, but also because of the transfusion-associated risk.¹⁻⁶ Therefore, several guidelines from various scientific societies have been issued, and all agree on making it mandatory to implement in clinical practice a patient blood management (PBM) strategy to prevent bleeding and to reduce blood product transfusion.⁷⁻¹¹

PBM is structured as a 3-pillar concept: (1) optimizing red blood cell mass, (2) minimizing blood loss, and (3) managing anemia.⁷⁻⁹ However, little consideration has been given to the characteristics of postoperative bleeding itself. In the universal definition of perioperative bleeding (UDPB), proposed by a group of international experts, chest tube drainage was taken into account along with 8 other clinical variables, and only blood volume at the end of the first 12 postoperative hours was recorded.¹² Very few studies have addressed bleeding kinetics in chest tubes,¹³⁻¹⁵ and postoperative hemorrhage level was defined arbitrarily by specific bleeding volume over fixed durations.¹³⁻¹⁵ We studied chest drainage, hourly, over

*Drs Gaudard and Colson are co-senior authors.

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Address correspondence to Dr Colson, Department of Anesthesiology and Critical Care Medicine, Arnaud de Villeneuve Academic Hospital, Montpellier University, 371 ave Doyen Giraud, 34295 Montpellier Cedex 5, France; email: p-colson@chu-montpellier.fr.

the first 12 postoperative hours. We also wondered whether bleeding volume at 12 postoperative hours could be predicted by bleeding during the very first hours after surgical procedures.

We designed a prospective observational study in adult cardiac surgical patients. The first objective was to describe bleeding kinetics during the first 12 hours. The second objective was to test a blood loss threshold within the first postoperative hours for detecting major bleeding (MB), defined as the upper 10th percentile of blood loss at 12 hours.

Patients and Methods

Trial Design

This was a prospective, single-center, observational study. The study protocol was approved by the Institutional Review Board of Montpellier University Hospital Center, Montpellier, France (2016-A00170-51) and registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT02712879, June 13, 2016). Patients were formally informed, but the need for written informed consent was waived by regulatory authorities because of the observational design of the study.

Patient Population

All adult patients (>18 years of age) who were consecutively admitted from January to June 2016 to the postoperative intensive care unit (ICU) of a tertiary academic hospital after elective or emergency cardiac surgical procedures that was performed using cardiopulmonary bypass were included. Patients operated on for cardiac transplantation or left ventricular assist device placement were excluded because these cases are not routine in all cardiac surgical procedures centers.

Patients who underwent early reoperation for surgical hemostasis within the first 12 postoperative hours were excluded from the final analysis because these patients had threatening bleeding with hemodynamic instability resulting from either hemorrhagic shock or cardiac tamponade.

Interventions

DEFINITION OF CHEST TUBE BLEEDING. Bleeding was quantified as the amount of blood collected by thoracic drains inserted during the surgical procedures. Tube drains included pericardial and mediastinal drains and, when appropriate, pleural drains. Volume collection was routinely recorded every hour and then was adjusted to the patient's weight (mL/kg/h).

To avoid clogging of drainage tubes, nurses were asked to perform an aspiration maneuver if no blood was collected. All patients had repeated echocardiographic examinations, either to check cardiac function or to detect cardiac tamponade.

PATIENT MANAGEMENT AND DATA COLLECTION. Data on demographic characteristics, medical history, organ function according to standard assessment, and active treatment for coagulation were collected. Preoperative blood samples collected in routine practice provided blood count values and determinations of homeostatic function.

The indication for the surgical procedures and its context were recorded. Surgery and cardiopulmonary bypass were carried out as routinely and according to the PBM protocol in use in the institution. PBM included an anticoagulation protocol with the heparin or protamine dose adjusted by monitoring of activated clotting time (Hepcon HMS, Medtronic, Minneapolis, MN), systematic use of tranexamic acid administration and a cell-saving device during the perioperative period, point-of-care coagulation monitoring in case of bleeding (viscoelastic measurements, TEG, Haemonetics, Braintree, Massachusetts), and predefined algorithms of blood product administration or coagulation drugs.

Laboratory data, including hemoglobin, platelet, fibrinogen, and coagulation test results, were collected on arrival in the ICU. The blood loss in the chest tube drains was recorded every hour during the first 12 hours. Blood products, hemostatic treatments, and requirement of revision surgical procedures were recorded. Hemodynamic instability was defined by the need for hemodynamic support (introduction of inotropic or vasopressor therapy or increase in administered dose by more than 20%).

Follow-up monitoring included the following: hospital death; length of ICU and hospital stays; and incidence of complications, defined as atrial fibrillation, cardiac dysfunction if 2 inotropic agents or cardiac assistance were required, renal failure according to Kidney Disease: Improving Global Outcomes criteria, pulmonary dysfunction (artificial ventilation >24 hours or a ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen <200), liver dysfunction (plasma hepatic enzymes or bilirubin more than twice the standard value), and hematologic dysfunction (platelet count <80 G/L). The Simplified Acute Physiology Score II within the first 24 hours in the ICU was determined on ICU admission.

End Points

The primary end point was to describe, hour by hour, bleeding kinetics during the first 12 postoperative hours. Secondary end points were as follows: (1) to estimate within the first postoperative hours a blood loss threshold for detecting MB, defined by postoperative bleeding exceeding the 90th percentile at 12 postoperative hours; and (2) to compare perioperative characteristics of patients with MB with those of standard patients.

Sample Size Calculation

To classify at least 30 patients as having MB, we needed to collect data from at least 300 patients.

Statistical Analysis

Continuous variables were described as mean and SD or median and first and third quartiles [Q25 to Q75]. Categorical variables were described as frequencies (n) and percentages.

Postoperative bleeding kinetics was studied with a curve fitting analysis, by testing linear, exponential or logarithmic, or polynomial functions. The curve fitting with the best determinant coefficient (R^2) was selected.

A receiver operating characteristics curve analysis was then performed to determine a predicted bleeding threshold of MB with the best sensitivity, specificity, positive predictive value, and negative predictive value. Areas under the curve were calculated using the trapezoidal method of Wilcoxon and were expressed as mean value with 95% confidence interval.

Mann-Whitney Wilcoxon tests for quantitative variables and χ^2 or Fisher exact tests for categorical variables were used to determine differences in unadjusted preoperative, perioperative, and postoperative characteristics between patients with MB and other patients.

All tests were 2-sided. A *P* value of less than .05 was considered to be significant for all statistical tests, but it was adjusted by Bonferroni correction in case of repeated comparison. Statistical calculations were performed using XLStat software version 7.5.2, Addinsoft, Brooklyn, NY).

Results

Study Population

During the survey period, 303 patients, 66 ± 12 years of age, 88 female and 215 male, underwent cardiac surgical procedures. Demographic data and characteristics of the surgical procedures are reported in Table 1. Eleven (3.6%) patients needed early reoperation for hemorrhagic shock ($n = 7$; median bleeding at 12 postoperative hours, 1913 mL [interquartile range (IQR), 1515, 2210]) or cardiac tamponade ($n = 4$; median bleeding at 12 postoperative hours, 570 mL [interquartile range, 545, 607] and were not included in the final analysis.

Chest Tube Bleeding

DEFINITION OF THE MAJOR BLEEDING GROUP. Chest tube bleeding at 12 postoperative hours recorded in 292 patients ranged from 60 to 2190 mL (median, 350 mL). Percentile distribution showed a good exponential fitting with a determination coefficient ($R^2 = 0.98$) for the whole

Table 1. Patient and Surgical Characteristics

Characteristics	Total N = 303	Standard n = 262	MB n = 30	<i>P</i> ^a
Demographics and medical history				
Male	209 (69)	189 (72)	20 (67)	.527
Age, y	68 [59, 74]	68 [59, 74]	67[61, 74]	.856 ^b
Weight, kg	75 [67, 86]	75 [67, 86]	77 [70, 89]	.652 ^b
Height, cm	170 [164,176]	170 [164, 176]	174 [164, 180]	.184 ^b
BMI, kg/m ²	26.0 [20.0, 29.4]	26 [23.3, 29.3]	25.4 [23.3, 29.5]	.87 ^b
Hypertension	165 (55)	143 (56)	22 (73)	.054 ^c
Atrial fibrillation	53 (17.5)	47 (18)	6 (20)	.803 ^c
Diabetes	78 (26)	70 (27)	8 (27)	>.999 ^c
COPD	27 (9)	25 (9.5)	2 (7)	>.999 ^c
PVD or stroke	62 (21)	56 (21)	6 (20)	>.999 ^c
Aspirin	196 (65)	172 (66)	24 (80)	.151 ^c
Dual APT	37 (12)	32 (12)	5 (17)	.559 ^c
Surgery				
Procedures				
CABG ^d	159 (53)	137 (52)	22 (73)	.033 ^c
Aortic valve ^d	106 (35)	91 (35)	15 (50)	.111 ^c
Mitral valve ^d	51 (17)	48 (18)	3 (10)	.319 ^c
Tricuspid valve ^d	32 (11)	30 (11.5)	2 (7)	.552 ^c
Aortic dissection	13 (4)	8 (3)	5 (17)	.006 ^c
Other	51 (17)	40 (15)	11 (37)	.009 ^c
Context				
EuroSCORE II, %	2.5 [1.3, 6.0]	2.4 [1.2, 6]	3.0 [1.7, 6.3]	.173 ^b
Combined surgery	101 (33)	82 (31)	19 (63)	<.001 ^c
Redo surgery	12 (4)	11 (4.2)	1 (3.3)	1 ^c
Urgency or emergency	38 (13)	28 (11)	10 (33)	.002 ^c

^a*P* value for comparison between standard patients and patients with MB; ^bMann-Whitney Wilcoxon test; ^c χ^2 or Fisher exact test; ^dSurgical procedures: each type is a cumulative number of all procedures, either alone or combined with another, and elective or emergency.

Values are n (%) or median [25, 75 interquartile range].

APT, antiplatelet therapy; BMI, body mass index; CABG, coronary artery bypass graft; combined surgery, more than 1 surgical procedure during the same operation; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MB, major bleeding; PVD, peripheral vascular disease.

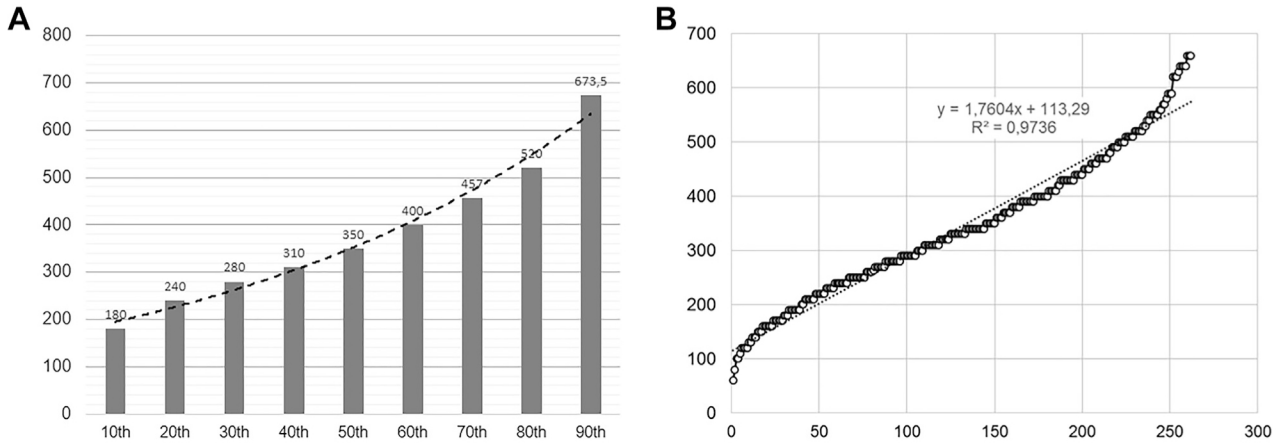


Figure 1. Distribution of cumulative bleeding at the 12th postoperative hour. (A) Percentile distribution of the cohort of all patients. Percentile distribution shows a good exponential fitting ($y = 168.85e^{0.1472x}$) (dashed line), with a determination coefficient of $R^2 = 0.98$. (B) Individual chest tube bleeding distribution up to the upper 10th decile has a linear fitting ($y = 1.7604x + 113.29$; $R^2 = 0.97$) (dotted line).

series, but a linear fitting ($R^2 = 0.97$) up to the upper 10th decile of the distribution (Figure 1). The upper 10th decile of the distribution corresponded to a threshold of 675 mL.

BLEEDING KINETICS. Bleeding kinetics is reported in Figure 2A. Bleeding decrease fits a logarithmic trend ($R^2 = 0.96$); 54% [IQR, 45% to 63%] of the bleeding volume occurred within the first 4 hours. Bleeding was significantly greater in patients with MB than in standard patients (Figure 2B).

Overall, the bleeding kinetics was similar in both groups: bleeding at 4 postoperative hours exceeded 50% of bleeding at 12 postoperative hours (54% [IQR, 45% to 63%] in standard patients vs 57% [IQR, 45% to 68%] in patients with MB ($P = .30$).

CHEST TUBE BLEEDING PREDICTIVE VALUE OF MAJOR BLEEDING. Because most of the bleeding occurred within the first 4 hours, we tested bleeding flow during this period to ascertain a predictive blood loss threshold to detect MB. Bleeding during each hour showed a decrease in the area under the receiver operator characteristics curve from hour 1 to hour 4 (Table 2). Bleeding predictive value

increased with cumulative volume until hour 4 and was already good at hour 2 (area under the curve, 0.87) with a threshold of 2.73 mL/kg (Table 2, Figure 3).

Comparison Between Standard Patients and Patients With Major Bleeding

Standard patients and patients with MB were not significantly different with regard to demographics and preoperative medical history, but they were different according to surgical procedure and complexity (Table 1). A high proportion of patients with MB underwent coronary artery bypass graft surgical procedures (Table 1) but elective coronary artery bypass grafting was more frequent in standard patients than in patients with MB: 218 (83.2%) vs 15 (50%), respectively ($P < .001$). Cardiopulmonary bypass and aortic cross-clamping times were significantly longer in patients with MB: cardiopulmonary bypass time: 98 minutes [IQR, 78, 139 minutes] vs 168 minutes [IQR, 102, 231minutes] for standard patients vs patients with MB, respectively ($P < 0.001$); and aortic cross-clamping time: 74 minutes [IQR, 54; 102 minutes] vs

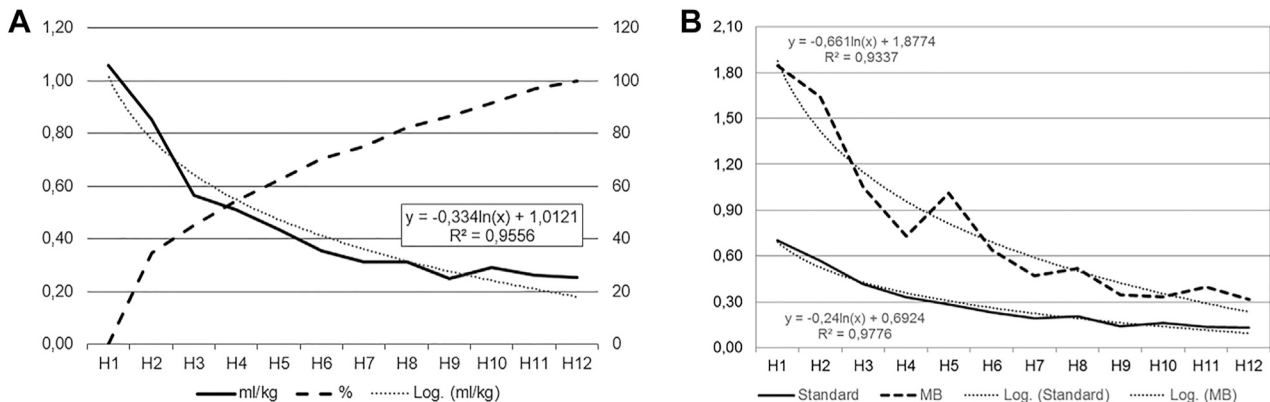


Figure 2. Chest tube bleeding kinetics. (A) Bleeding kinetics during the first 12th postoperative hour, expressed as mL/kg/h (left Y axis) and cumulative bleeding expressed as percentage of blood volume (right Y axis) at hour (H) 12. (B) Bleeding kinetics during the first 12th postoperative hour, expressed as mL/kg/h. Comparison between standard patients and patients with major bleeding (MB) ($P < .004$ at each time period).

Table 2. Predictive Value of Early Blood Loss for Major Bleeding^a

Time	Threshold mL/kg	Se	Sp	PPV	NPV	ROC AUC	95% CI	P
H1	1.08	0.83	0.73	0.25	0.98	0.81 ± 0.05	0.72-0.91	<.001
H2	0.95	0.87	0.79	0.31	0.98	0.84 ± 0.04	0.76-0.93	<.001
H3	0.74	0.67	0.79	0.26	0.96	0.75 ± 0.06	0.64-0.86	<.001
H4	1.02	0.47	0.94	0.44	0.94	0.71 ± 0.06	0.60-0.83	<.001
H1-H2	2.73	0.73	0.89	0.42	0.97	0.87 ± 0.04	0.79-0.94	<.001
H1-H3	3.96	0.77	0.92	0.52	0.97	0.87 ± 0.04	0.79-0.95	<.001
H1-H4	4.6	0.77	0.92	0.53	0.97	0.90 ± 0.04	0.83-0.97	<.001

^aBlood loss threshold at each postoperative hour (H), or cumulative blood loss at H2 (H1 to H2), H3 (H1 to H3), or H4 (H1 to H4); P value vs null hypothesis.

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC AUC, area under the receiver operating characteristics curve; Se, sensitivity; Sp, specificity.

111 minutes [IQR, 81; 183 minutes] for standard patients vs patients with MB, respectively ($P < .001$). Chest closure was delayed to ensure bleeding control in 6 patients of each group (2.3% vs 20%, between standard patients and patients with MB, respectively; $P < .001$).

Patient management during surgical procedures showed significant differences in fluid volume and blood product administration (Table 3). Patients with MB received more fluids, including colloids and blood products (Table 3). On arrival in the ICU, standard laboratory tests showed coagulation factors in a good range but at a slightly lower concentration in the MB group (Table 3).

In the ICU, management of bleeding resulted in higher transfusion rate in patients with MB (Table 3).

Follow-up showed significant differences between standard patients and patients with MB (Supplemental

Table 1). The in-hospital mortality rate was 2.6% ($n = 7$) vs 12.5% ($n = 3$) for standard patients vs patients with MB, respectively ($P = .005$).

Comment

In this single-center study, we analyzed bleeding after cardiac surgical procedures during the first 12 postoperative hours in a dynamic way, hour by hour. Bleeding volume declined logarithmically over time, with the majority of the bleeding volume occurring within the first 4 hours. MB, defined as the 10th upper percentile of bleeding at 12 postoperative hours, could be predicted with good accuracy by bleeding at hour 2 that was greater than 2.73 mL/kg. This threshold may help to detect patients at risk of MB early, to initiate a proactive strategy.

Figure 3. Receiver operating characteristics (ROC) curves for cumulative bleeding during the first 4 hours: hour (H) 2 (light gray) (H1 to H2), H3 (dark gray) (H1 to H3), and H4 (black) (H1 to H4). Areas under the receiver operating characteristics curves were 0.87 ± 0.04 ; (95% confidence interval [CI], 0.79 to 0.94), 0.87 ± 0.04 (95% CI, 0.79 to 0.95), and 0.90 ± 0.04 (95% CI, 0.83 to 0.97) for H1 to H2, H1 to H3, and H1 to H4, respectively ($P = .04$ between H1 to H2 and H1 to H4; $P = .68$ between H1 to H2 and H1 to H3; $P = .11$ between H1 to H3 and H1 to H4).

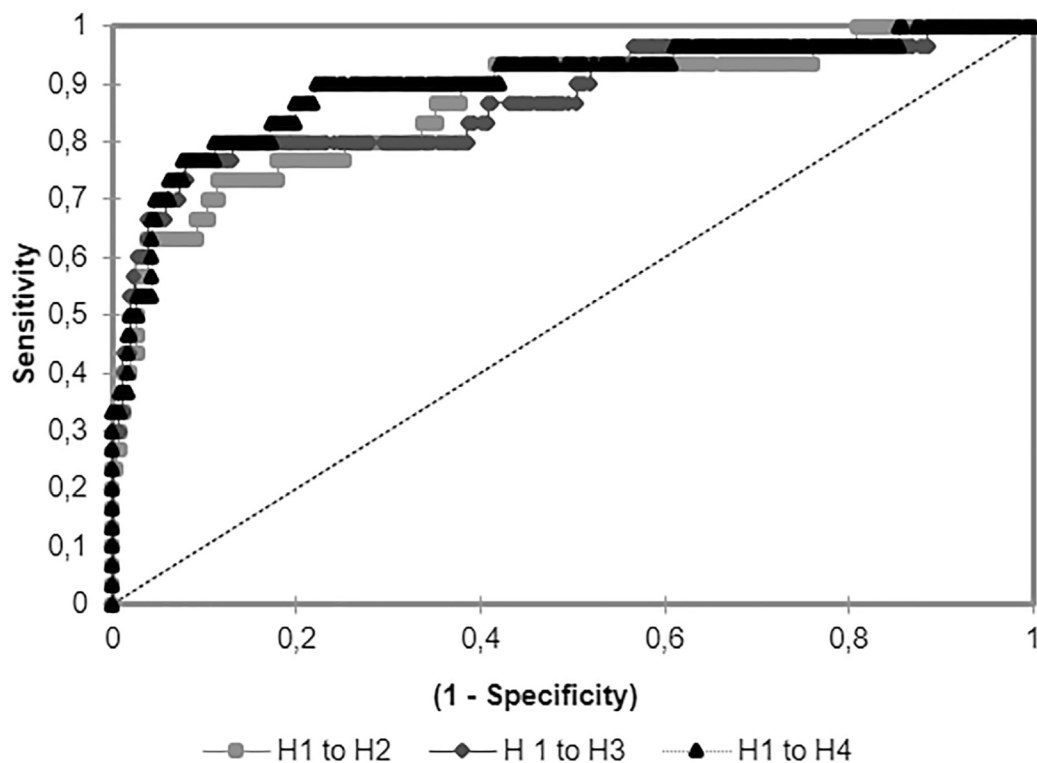


Table 3. Patient Management

Management	Standard	MB	P
Management during surgery			
Fluid volume, mL	4846 [4220, 5629]	5758 [5330, 7000]	<.001
Colloids, mL	0 [0, 0]	0 [0, 0]	.003
Patients	20 (8)	7 (23)	.012
Nadir Hb, g/dL	8.6 [7.7, 9.8]	8.1 [7.2, 9.7]	.111
Transfusion in operating room			
RBC	46 (7)	11 (36)	.025
FFP	18 (7)	11 (42)	<.001
Platelet concentrate	11 (4)	10 (33)	<.001
Fibrinogen	14 (5)	8 (27)	<.001
Biology in ICU			
Hb, g/dL	11.2 [10.3, 12.2]	10.7 [9.9, 11.6]	.021
Prothrombin time ratio, %	81 [73, 88]	75 [70, 81]	.01
<50%	4 (1.5)	1 (3.3)	.421
Platelets, G/L	154 [133, 190]	140 [105, 194]	.09
<50 G/L	1 (0.4)	1 (3.3)	.195
Fibrinogen, g/L	2.7 [2.4, 3.4]	2.5 [2.1, 3.0]	.073
<1.5 g/L	4 (1.5)	3 (10)	.023
Transfusion in ICU			
RBC	19 (7)	9 (30)	<.001
FFP	3 (1)	2 (6.7)	.084
Platelets concentrate	2 (0.7)	2 (6.7)	.109
Fibrinogen	0 (0)	3 (10)	.001
Protamine	25 (9.5)	19 (63)	<.001
Biology at day 1 in ICU			
Hb, g/dL	11.4 [10.4, 12.3]	10.6 [9.7, 11.6]	.002
Prothrombin time ratio, %	90 [80, 99]	80.5 [76, 88]	<.001
<50%	2 (0.8)	0 (0)	>.999
Platelets, G/L	170 [143, 207]	148 [118, 237]	.39
<50 G/L	2 (0.8)	1 (3.3)	.279
Fibrinogen, g/L	4.1 [3.6, 4.6]	3.7 [3.3, 5]	.121
<1.5 g/L	0 (0)	1 (3.3)	.103

Values are n (%) or median [25, 75 interquartile range].

FFP, fresh frozen plasma; Hb, hemoglobin; ICU, intensive care unit; MB, major bleeding; RBC, packed red blood cells.

In previously published studies, blood loss from chest drains for assessing bleeding after surgical procedures has not been reported consistently. In the experts' proposal of the UDPB, blood loss volume was checked only at the 12th postoperative hour.¹² In their validation cohort, blood loss volume influenced the ranking in only 16.7% of all the bleeding patients.¹² Indeed, hourly bleeding has been scarcely studied, moreover over short periods of observation. To elaborate on the preoperative bleeding score, Vuylsteke and colleagues¹³ used a threshold of 2 mL/kg/h during 3 hours or less, along with a specific transfusion requirement. Predefined bleeding rates have been studied, either during 6 consecutive hours (>1.5 mL/kg/h)¹⁵ or during 2 hours within the first 6 hours (2 mL/kg/h).¹⁴ These 2 studies allowed identification of actively bleeding patients, and both studies showed that these patients had more complicated postoperative outcomes.

Using hourly bleeding allowed us to obtain a more comprehensive picture of postoperative bleeding. We excluded from the final analysis patients who underwent reoperation for surgical hemostasis because it could have resulted in bias in bleeding volume assessment in the series. However, the incidence of reoperation for hemostasis (3.6%) was in the lower range of the rate reported elsewhere (1% to 11%).^{2,16,17}

In the remaining cohort, bleeding has an exponential distribution, with a marked increase in bleeding volume in the upper 10th decile of the distribution, which makes sense for defining MB, as done previously in a larger cohort.² The bleeding kinetics fit a logarithmic regression, meaning that blood loss declined quickly within the first postoperative hours. Blood loss was higher at each hour in the MB group, but it also decreased faster within the first 4 postoperative hours. Therefore, bleeding greater than 1 mL/kg at the first postoperative hour has already a

good negative predictive value (0.97), and within the first 2 hours, it could have been possible to rule out MB when blood loss was lower than 2.73 mL/kg, with only 11.4% error.

Besides higher postoperative bleeding volume, we observed that several surgical characteristics were significantly associated with MB. Indeed, patients with MB more often underwent complex surgical procedures, meaning combined procedures or emergency operations, than standard patients. These results are in agreement with previous studies aimed at elaborating risk scores of bleeding or transfusion.^{2,13,18-20} The transfusion requirement in the operating room, which is related to surgical procedures conditions as well, was also significantly higher in patients with MB. The cumulative consequences of bleeding, fluid loading including colloids,²¹ and transfusion may have contributed to the worse outcome observed in patients with MB when compared with other patients.² Interestingly, patients with MB had acceptable functional levels of hemoglobin, prothrombin time, or fibrinogen on admission to the ICU (Table 3), but these markers were in a lower range than in standard patients. Because these factors are crucial for the coagulation process,^{22,23} the study suggests that subnormal ranges may be not enough, possibly along with other undetected factors, to obtain appropriate coagulation in patients with MB.

Taken together, these observations suggest that MB at 12 postoperative hours can be predicted mostly in cases of an MB profile, which depends on the surgical procedures context (combined or emergency surgical procedures), the patient's intraoperative transfusion requirement, and a high bleeding volume at 2 hours. These results may encourage optimizing coagulation in these patients to reduce postoperative blood loss. However, further study is needed to demonstrate whether individualizing a transfusion strategy, including targeting supranormal plasma concentrations of coagulation factors, may have beneficial effects.²³

Study Limitations and Strengths

First, this was a single-center observational study. However, we believe that the use of a PBM strategy as recommended by international scientific societies tends to standardize practice among centers where such a strategy is implemented. Second, we chose to not include early reoperation. These patients did not compare with patients who had continuous bleeding; therefore, integrating reoperated patients' bleeding, which was interrupted by the reoperation, into the overall bleeding kinetics would have biased the results. Moreover, patients who underwent reoperation represented a small proportion of the cohort. Third, the MB definition resulted in bleeding volume in a low range of the UDPB (moderate to severe), but this may reflect the benefit of the PBM strategy. In any case, postoperative follow-up and outcomes showed significant differences between patients with MB and standard patients, an observation consistent with previous publications.

Conclusion

Using the hourly rate of chest tube blood loss within the first postoperative hours seems relevant to identify patients at risk of MB after cardiac surgical procedures. Further studies are needed to assess whether the early detection of patients with major bleeding will eventually improve blood conservation strategies and patient outcomes.

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